UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION **This Document Relates to All Actions**	MDL No. 2875 Honorable Robert B. Kugler, District Court Judge

DECLARATION OF GEORGE E. JOHNSON, Ph.D.

I, George E. Johnson, Ph.D. submit the following declaration to respond to the critiques set forth in plaintiffs' motion to exclude my opinions. This declaration is based upon well-founded medical and scientific principles and my scientific experience.

1. I am over 18 years of age and am a full Professor of Toxicology at Swansea University. My academic and professional background are addressed in Section 2 of my amended expert report served on October 1, 2021.

2. In my evaluation and analysis of this matter I utilized the same methodology and scientific analysis that I use in my professional life as an active toxicology researcher and scientific journal reviewer, and applied my education, training, and experience in toxicology to my analysis.

3. This evaluation includes a calculation of the Permissible Daily Exposure ("PDE") for these impurities utilizing the Benchmark Dose ("BMD") method.

4. In May 2021 my article *Permitted daily exposure limits for noteworthy N-nitrosamines* was published in the peer reviewed journal Environmental and Molecular Mutagenesis. Following International recommendations (ICHM7; ICHQ3C and ICHQ3D) this study calculated permissible daily exposures (PDE) for NDMA and NDEA using published rodent cancer bioassay and in vivo mutagenicity data. The PDE for NDMA I determined in the study is

higher than the acceptable daily intake ("AI") for NDMA and NDEA calculated by FDA using simple linear extrapolation from animal carcinogenicity data. The first draft of the May 2021 article was submitted for review in January 2019. I presented my BMDL (benchmark dose level) and PDE analysis of NDMA and NDEA numerous times in 2019 to various scientific and regulatory audiences where the specific PDE levels and calculations contained in my report in this case were discussed.

The Benchmark Dose Approach Used to Calculate the PDE for NDMA and NDEA is Based on Decades of Research and Widely Accepted in the Scientific Community.

5. The BMD approach I applied in the study to determine the PDE is not "investigational" or "experimental". It is widely accepted by the scientific community and has been for nearly a decade as evidenced by countless peer reviewed articles.[1] Plaintiffs statement that no other studies in my expert report are cited for authority to calculate a PDE for NDMA is not accurate.

6. The BMD approach for determining a PDE is recognized by the FDA in its Guidance that adopts the ICH M7 regulations which specifically permits the PDE methodology when assessing risk of chemical impurities in drugs, including mutagenic impurities which are otherwise not subject to the Threshold of Toxicological Concern (TTC) "*where there is an established threshold mechanism"*.[2] According to the ICH M7:

"The existence of *mechanisms* leading to a dose response that is *non-linear* or has

[1] By way of example, see *MacGregor, 2015b* ("The BMD approach was considered to be the preferred approach for dose(exposure)-response analysis and the PoD derivation for genotoxicity data…") *(co-authors include Dr. Johnson, FDA, EPA, Health Canada, Japan); 2016 Dearfield*, et al. "The BMDL was determined to be the most robust and conservative and is recommended for general use as the PoD (Point of Departure) for genetic toxicity testing analysis." *co-authors include Dr. Johnson, FDA, EPA, Health Canada, Japan)*

[2] ICHM7. (2017). M7 (R1): *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.* The ICH M7 is incorporated in FDA's *Guidance on Nitrosamines.*

> a *practical threshold*, is increasingly recognized, not only for compounds that interact with non-DNA targets but also for DNA reactive compounds, whose effects may be modulated by, for example, rapid detoxification before coming into contact with DNA, or by *effective repair* of induced damage. The regulatory approach to such compounds can be based on the identification of a No-Observed Effect level (NOEL) and use of uncertainty factors (see ICH Q3C(R5)), to calculate a permissible daily exposure (PDE) when data are available." ICHM7(R1) (2017).

7. In other words, according to the harmonized regulations adopted by FDA, the PDE approach I employed may be implemented for a DNA-reactive mutagenic compounds like NDMA and NDEA, if there is a showing that there exists a biological threshold mechanism to modulate the compounds at low levels. Here, this requirement has been met as evidenced by numerous peer reviewed studies demonstrating the specific repair mechanism for NDMA-induced mutations.[3]

8. FDA, EMA (Europe), Health Canada, PMDA (Japan), Therapeutic Goods Administration (Australia) all accept the use of PDE calculations in certain instances based on the ICH 7 guidance, which harmonizes these regulatory bodies:

> "The BMD approach was considered to be the preferred approach for dose (exposure)-response analysis and the PoD ["point of departure"] derivation for genotoxicity data…"there was agreement that the BMD analysis is suitable for defining PoD's for genetic toxicology data for both discrete (quantal) and continuous responses. Based on experience to date with continuous data, benchmarks defined as a specified increase relative to background appear to have the greatest acceptance with respect to the analysis of genetic toxicology data…" *2015 MacGregor b (co-authors include Dr. Johnson, FDA, EPA, Health Canada, Japan)*

[3] Arimoto-Kobayashi S, Kaji K, Sweetman GM, Hayatsu H. Mutation and formation of methyl- and hydroxylguanine adducts in DNA caused by N-nitrosodimethylamine and N-nitrosodiethylamine with UVA irradiation. Carcinogenesis. 1997 Dec;18(12):2429-33. doi: 10.1093/carcin/18.12.2429. PMID: 9450491; White PA, Long AS, Johnson GE. Quantitative Interpretation of Genetic Toxicity Dose-Response Data for Risk Assessment and Regulatory Decision-Making: Current Status and Emerging Priorities. Environ Mol Mutagen. 2020 Jan;61(1):66-83. doi: 10.1002/em.22351. Epub 2019 Dec 19. PMID: 31794061.

The MGMT Repair Enzyme is Well-Established As the Threshold Mechanism for the DNA Repair of Mutations Resulting from Exposure to NDMA and NDEA.

9. FDA's *Control of Nitrosamines* appendix states the TD50 linear extrapolation is appropriate where there is no established threshold *mechanism* (emphasis added). That is correct – but for NDMA and NDEA, unlike many compounds in the Cohort of Concern, there is an established threshold mechanism – it is the DNA repair effected by the MGMT enzyme. That mechanism is well-studied and has been published in many peer reviewed journals. The DNA repair mechanism, and the capacity of this mechanism to result in the NDMA and NDEA dose-response is well established. In my report I addressed the issue of MGMT threshold in order to support my opinion that at the level of exposure of NDMA in the valsartan is within the daily capacity of the liver to repair any mutations from the NDMA. The DNA repair mechanism and capacity of this mechanism to result in the NDMA threshold dose is well established. MGMT deficiency is covered by the adjustment factors in the BMDL and PDE calculation.

10. Plaintiffs' statement that the PDE methodology conflicts with the methodology that is generally accepted to determine safe levels of NDMA in drugs is incorrect and misleading. The PDE method is not in conflict where, as in this case, there **is** sufficient data to establish the threshold mechanism for NDMA and thus apply the more precise PDE calculation.[4]

The FDA's AI for NDMA and NDEA is a Conservative and Theoretical Calculation that Does Not Consider the Human DNA Repair Mechanism or Capacity and Does Not Address the General Causation Question in this Litigation.

11. FDA's Acceptable Intake (AI) based on the TD50 has no adjustment to humans at all. It is not a precise measure of human risk of cancer as the PDE for NDMA/NDEA is. The values

[4] See, Jiao, et al, (1997) *Analysis of tissue-specific lacZ mutations induced by N-nitrosodibenzylamine in transgenic mice*. Carcinogenesis 18: 2239-22445; Gollapudi, et al. *Hepatic lacI and cII mutation in transgenic rats treated with NDMA*, Mutat. Res. 419:131-135

entirely relate to the rodents and not to humans. But the calculation produces low numbers, i.e. very conservative numbers not based on humans, and is meaningless from an actual risk assessment as it pertains to NDMA and NDEA. The FDA's linear approach assumes that DNA damage is directly proportional to the dose, and high dose animal studies are simply extrapolated to low doses without any experimental evidence. It suggests there is 'no safe dose' which ignores the DNA repair capacity that prevents the linear dose response by dampening or diminishing the response curve.

12. The linear approach employed by FDA in determining the (AI) for NDMA and NDEA ignores the body's capacity to mitigate DNA damage from mutagenic substances which have evolved to cope with the daily exposure to dietary and endogenous nitrosamine production. This is particularly true at low doses of mutagenic exposure, as DNA repair has evolved to deal with constant low-level DNA damage induction.[5] Accordingly it is scientifically unfounded to assume that mutagens like NDMA and NDEA cause DNA damage in a linear fashion like the AI approach assumes. All experimental evidence is to the contrary.

13. There are numerous examples of DNA-reactive substances that have nonlinear dose responses. Many of these are from standard study designs using the BMD approach, and there are also extensive dose responses for use in defining BMD confidence intervals (CI) with high precision. Based on my study and other peer-reviewed publication there is an established threshold mechanism for NDMA and NDEA – it is the MGMT 'suicide' repair enzyme which specifically effects a complete repair of the specific DNA adduct (O6 MeG) known to be caused by the NDMA metabolite. That mechanism is well-studied and has been published in many peer reviewed

[5] Teasdale, A., Mutagenic Impurities: Strategies for Identification and Control, (2022), Sec. 8.1.2,

journals.[6] The mechanism and capacity of the mechanism for the NDMA and NDEA threshold dose-response via DNA repair permits the application of the BMDL approach as outlined by the ICH M7.

14. My PDE calculation using 100 kg patients was based upon the specific patient population of the plaintiffs in this case for whom we had data, and the average weight of that population was approximately 100 kg – nowhere near the 50 kg the FDA used in their AI (Acceptable Daily Intake) calculation. It is not either unacceptable or stealthy to use the 100 kg value – it is factual. The resulting PDE from the BMDL CI (Benchmark Dose Method with a confidence interval) for 50 kg through 100 kg patients covered nearly all of the batches of valsartan tested. There were limited examples of batches that were within 1 magnitude (x10) of the PDE confidence intervals. It is assumed that plaintiffs had different batches throughout their treatment, which would affect the mean intake.

15. Neither in my report nor deposition have I stated that there is "no risk" from NDMA or NDEA, my opinion stated in my report is that there is no increased risk of cancer from the exposure to the trace levels of impurities detected in valsartan. Studies have established that the NDMA-specific adducts and mutations are always occurring in cells and the body's defense

[6] Fahrer J, Frisch J, Nagel G, Kraus A, Dörsam B, Thomas AD, Reißig S, Waisman A, Kaina B. DNA repair by MGMT, but not AAG, causes a threshold in alkylation-induced colorectal carcinogenesis. Carcinogenesis. 2015 Oct;36(10):1235-44. doi: 10.1093/carcin/bgv114. Epub 2015 Aug 4. PMID: 26243310. White PA, Long AS, Johnson GE. Quantitative Interpretation of Genetic Toxicity Dose-Response Data for Risk Assessment and Regulatory Decision-Making: Current Status and Emerging Priorities. Environ Mol Mutagen. 2020 Jan;61(1):66-83. doi: 10.1002/em.22351. Epub 2019 Dec 19. PMID: 31794061; Lutz Müller, Elmar Gocke, Thierry Lavé, Thomas Pfister; Ethyl methanesulfonate toxicity in Viracept—A comprehensive human risk assessment based on threshold data for genotoxicity, Toxicology Letters, Volume 190, Issue 3, 2009; Bernd Kaina, Markus Christmann, Steffen Naumann, Wynand P. Roos, MGMT: Key node in the battle against genotoxicity, carcinogenicity and apoptosis induced by alkylating agents, DNA Repair,Volume 6, Issue 8, 2007, Pages 1079-1099.

mechanism vis-à-vis the MGMT repair enzyme repairs those mutations. The capacity of the liver containing this DNA repair mechanism is sufficient to address DNA adducts which may result from the level of NDMA and NDEA detected in valsartan.

16. Plaintiffs incorrectly criticize my report for not including a capacity value, i.e. a threshold limit of the body's DNA repair system to modulate the risk of exposure to a certain point. That capacity is defined both by the capacity to metabolize and the capacity to repair mutations. The PDE I calculated in the study published in 2021 demonstrates that the level of NDMA and NDEA in the valsartan for this patient population is within the liver's capacity to repair any resulting DNA adducts, and the maximum capacity of the liver to handle NDMA-induced DNA adducts was not necessary to determine in order to conclude these trace levels do not increase the risk of cancer in these patients.

Dietary Studies Are Too Imprecise to Be Incorporated Into a General Causation Opinion on Toxicology.

17. The PDE calculations in my report and the May 2021 publication do not include dietary studies because dietary studies include too many variables including hundreds of other probable human carcinogens in the diet and poor, imprecise measures of NDMA exposure, through questionnaires alone, and the studies are not useful for this current risk assessment where precision in the NDMA levels is required in order to define a human exposure limit. Dietary studies all contain reliance-limiting caveats that other variables cannot be disregarded, including a failure to account for lifestyle factors, and therefore the data in those studies are not useful for calculating human exposure limits, which is why they also do not inform and are not considered in the (AI) determined by the FDA. Simply put, the correlations reported in the dietary studies is not causation.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

GEORGE E. JOHNSON, Ph.D.

Signature

2/24/2022

Date